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ROLE OF D-2 RECEPTORS IN NEUROTENSIN RELEASE INDUCED BY A LOW DOSE OF METHAMPHETAMINE.

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Neurotensin (NT) is thought to act as a modulator of central dopamine (DA) systems, and is closely associated with DA in the nigrostriatal and mesolimbic pathways. Numerous studies have investigated the effects of microinjected NT on the activity of these DA systems. Although several studies have shown that NT is excitatory on DA neurons, the overall effect of injected NT seems to antagonize DA-enhancing drugs. However, its regulation by DA has been limited to assessing alterations in peptide tissue levels or mRNA following lesions or pharmacological manipulations of dopaminergic pathways. Due to the relatively large molecular size and low quantity of NT, measurement of its release has been difficult. We previously reported methodology allowing the measurement of in vivo release of NT by microdialysis. It was further shown that the DA D-2 agonist quinpirole and a low dose (0.5 mg/kg) of methamphetamine (METH) increased the extracellular concentration of NT in the striatum and nucleus accumbens. Quinpirole increased extracellular NT to ≈225% of control in the striatum, and ≈150% of control in the accumbens, while METH increased extracellular NT to ≈200% of control in both structures. These effects may indicate a possible role of D-2 receptors in mediating the effects of low doses of METH on NT release. To test this hypothesis, we combined METH with the D-2 antagonist eticlopride (0.5 mg/kg). Eticlopride by itself decreased extracellular concentrations of NT in both the striatum and nucleus accumbens by 20-35%. When combined with METH, eticlopride completely blocked the increase in NT release caused by METH alone. Thus, stimulation of D-2 receptors by either direct or indirect agonists increases the release of NT, and this effect can be completely abolished by concurrent blockade of D-2 receptors. (This work was supported by USPHS grants DA 09407 and DA 00869).

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A COMPARISON BETWEEN IMMEDIATE AND LATE ADMINISTRATION OF CNTF ON PERIPHERAL NERVE REGENERATION.

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Ciliary neurotrophic factor (CNTF) has emerged in the last 15 years as one of the most potent agents in terms of nerve regeneration. It is an acidic protein containing 200 amino acids and was isolated from concentrated extracts of chick intraocular tissue by Mathorpe et al. (1980).[1] Its gene sequence has been cloned from rat, rabbit and human sources.[2] CNTF was first observed to support the survival of ciliary ganglia of the chick's parasympathetic nervous system in vitro. In vivo, exogenous administration of CNTF reduces programmed cell death of chick motoneurons[3] and reduces the axotomy-provoked cell death of immature rat motoneurons[4]. CNTF immunoreactivity has been localized to the motoneurons of the peripheral nervous system and its production isolated to Schwann cells[5]. These observations have prompted us to further investigate the neurotrophic potential of CNTF using the nerve crush paradigm. In small clinical trials it was found that the effectiveness of CNTF on nerve regeneration is restricted due to the deleterious effect of CNTF on body weight. This may be due to the dosage, route, and pattern of administration of CNTF. Consequently, we have designed our animal studies to examine three low dosages of CNTF administered at different times during the regeneration process. With the dosages we have used (10, 20 & 40μg/kg) and with our pattern of administration (i.p. injection 0-8d or 10-18d) we find no significant weight change. Interestingly, our dosage and pattern of administration enhances regeneration in a manner similar to other laboratories that utilize dosages 10 times greater.[6] Since CNTF has tremendous clinical potential, we believe our results may contribute to a greater understanding of its efficacy as a therapeutic factor in diseases of the peripheral nervous system involving motoneurons.

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